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WHAT'S NEW IN INTENSIVE CARE

Vasoconstriction in septic shock

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Septic shock is associated with endothelial dysfunction leading to arterial and venous dilation, alterations in regional blood flow distribution, and microcirculatory disturbances. Fluids and vasopressors are the key elements of the hemodynamic support. Promoting vasoconstriction to correct hypotension goes well beyond the simple effect of counteracting arterial dilation. Vasopressors also impact heart function, the venous system, regional blood flow distribution and microvascular perfusion. These effects are discussed in this concise article, focusing on the most recent literature.

Generalized dilation in sepsis

Through various mechanisms, sepsis decreases vascular tone, inducing hypotension and decreasing tissue perfusion. In addition, regional blood flow distribution may be impaired. Regional perfusion is regulated by modulating regional arterial tone through constriction of some vascular beds and dilation of others, and this mechanism is altered in sepsis. Accordingly, splanchnic perfusion may be impaired even when cardiac output is maintained.

Microvascular perfusion may also be compromised, at least partly due to the impaired response to endogenous vasoconstrictive substances [1]. Venous dilation contributes to the hemodynamic alterations, redistributing blood from stressed to unstressed venous compartment, decreasing cardiac preload even when total blood volume is preserved [2].

Cardiovascular effects of vasopressors

The response of arterial tone to vasopressors may be blunted in sepsis due to decreased density and sensitivity of their respective receptors. Through venous constriction, vasopressors also redistribute blood from unstressed to stressed volume, potentiate fluid resuscitation by shrinking the venous reservoir and help reduce the fluid volume infused [3].

In addition, there is a mild inotropic effect for norepinephrine [4], which is stronger for epinephrine but absent for vasopressin and angiotensin. The impact of vasopressors on cardiac output varies according to the interaction between cardiac function, preload-responsiveness and changes in preload, afterload and heart rate (electronic supplementary material, ESM).

Impact on regional perfusion and microcirculation

The impact of vasopressors on regional circulations may depend on the agent as alpha adrenergic, vasopressin-1 and angiotensin-2 receptors are unequally distributed in the vascular tree. The density of vasopressin-1 receptors is higher on splanchnic vessels, so that vasopressin derivatives may decrease splanchnic blood flow. While detecting overt splanchnic ischemia is difficult, impaired gastric mucosal PCO_2 [5] or cytolysis during vasopressin infusion can suggest the impairment of mesenteric perfusion. Such events seem less frequent with norepinephrine [5] (ESM).

Vasopressin-1 and angiotensin-2 receptors are more numerous on efferent than afferent renal vessels, so that vasopressin and angiotensin may increase glomerular perfusion in septic shock. Accordingly, vasopressin reduces more requirements of renal replacement therapies than norepinephrine [6]. Similar effect seems to occur with angiotensin, but the evidence is still limited [7]. Vasopressors may also differently affect pulmonary vasculature (ESM).

The microcirculatory effects of vasopressors are difficult to predict. They may constrict resistance arterioles and thus decrease downstream capillary perfusion. Venous constriction also increases mean systemic filling pressure and hence venous pressure at the exit of capillaries. These combined effects may impair microvascular

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perfusion. On the other hand, vasoconstriction may counteract the excessive vasodilation in some capillaries, which contributes to microvascular dysfunction. In addition, restoring organ perfusion pressure may improve microvascular perfusion. Optimal macrohemodynamic targets to perfuse and recruit the microvessels may vary between patients and vascular beds.

In experimental sepsis, correction of severe hypotension was associated with improved microvascular perfusion [8]. In septic shock patients, the impact of correcting severe hypotension has not been tested. Increasing median arterial pressure (MAP) above 65 mmHg had variable microcirculatory effects (ESM). Similarly, norepinephrine heterogeneously improved skin perfusion as assessed by the capillary refill time [9]. Altogether this suggests that the MAP target should be individualized, avoiding both hypotension and excessive vasoconstriction, and aiming to improve tissue perfusion [10].

Which vasopressor should be selected?

Beyond their above-mentioned hemodynamic effects, vasopressors have many other effects (e.g., pro-arrhythmic, immunologic, metabolic and other cellular actions) depending on the stimulated vasopressor and non-vasopressor receptors. Norepinephrine is the first-line agent. While epinephrine generates similar vasoconstriction by stimulating the same alpha-adrenergic receptors, the associated beta-adrenergic stimulation may increase arrhythmias and generate imbalance between metabolism and perfusion, especially at high doses [11]. This makes sense for combining several vasopressors of different classes instead of further increasing the dose of the first agent when it is at reasonable doses but does not suffice. For each agent, the benefit/risk balance should be evaluated.

Vasopressin is an attractive alternative/adjunct to norepinephrine. Beyond its use in patients not responsive to norepinephrine, vasopressin induces less arrhythmias and improves renal function [6]. However, no difference in mortality is observed suggesting that other adverse events also take place (ESM). Accordingly, the choice of the vasopressor should be individualized [10].

Angiotensin has been recently reintroduced. In patients with persistent hypotension despite norepinephrine and/or vasopressin, addition of angiotensin increased MAP and spared other vasopressors [12]. The impact on outcome should be evaluated in larger trials.

The place of other agents remains to be determined (ESM). Methylene blue as a vasopressor in sepsis was first described at the end of the last century. More recently, several small, single-center randomized studies shed new light on it. Nevertheless, larger trials should confirm its safety as other agents interfering with the nitric oxide pathway have shown an increased mortality [13].

The place of hydrocortisone should not be neglected as it may potentiate the effects of vasopressors. Identifying patients who benefit from hydrocortisone in terms of survival and organ function remains a priority for future research.

When to initiate vasopressors?

Introduction of vasopressors is a challenging decision. On the one hand, early introduction may impair tissue perfusion if fluid resuscitation has not yet been completed. On the other hand, early vasopressors may increase preload and help restore perfusion pressure. In experimental conditions, immediate introduction of norepinephrine better preserved intestinal microcirculation [14]. An observational propensity matched study reported that early norepinephrine introduction reduces resuscitation fluid requirements and may be associated with improved 28-day mortality [3]. While similar beneficial effects of early vasopressor introduction are expected from other vasopressors, these have not been well evaluated. Factors identifying which patients may benefit from early or even immediate vasopressor therapy should be better determined [15].

When to stop vasopressors?

Weaning from vasopressors is another difficult task as hypotension episodes that often occur may unnecessarily prolong their administration. Computer-aided strategies may help achieving more rapid weaning from vasopressors. Measuring arterial elastance may guide weaning, but its ability (and cut-off) to predict weaning-associated hypotension varies between among studies. At this stage, this approach remains more conceptual than practical (ESM).

Take-home message

While restoring MAP is the first goal of vasopressor therapy, vasopressors use is also associated with beneficial effects on venous reservoir and usually on organ perfusion (Fig. 1). Nevertheless, excessive vasoconstriction should be avoided, and other resuscitation strategies should not be neglected. The various vasopressor agents have different physiological and non-vasopressor properties that should be considered to personalize vasoconstrictive therapies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-024-07332-8.

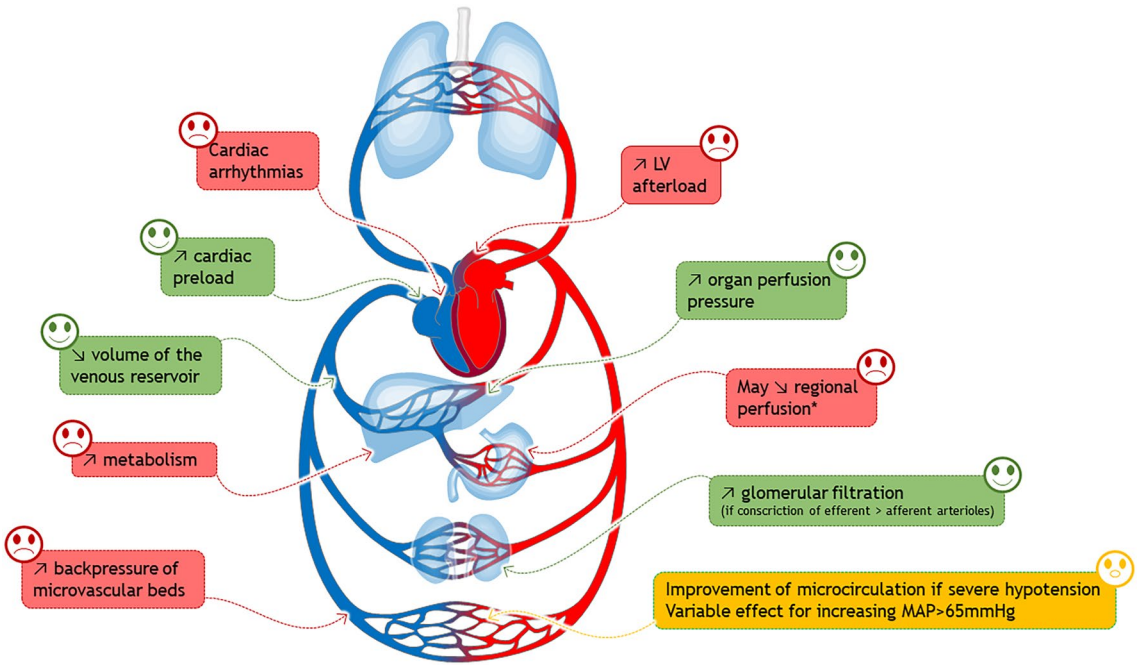
Cardiac arrhythmias
↗ LV afterload
↗ cardiac preload
↗ organ perfusion pressure
↘ volume of the venous reservoir
May ↘ regional perfusion*
↗ metabolism
↗ glomerular filtration
(if conscriction of efferent > afferent arterioles)
↗ backpressure of microvascular beds
Improvement of microcirculation if severe hypotension
Variable effect for increasing MAP>65mmHg

Fig. 1 The pros and cons of vasoconstriction in septic shock. The beneficial, variable and adverse effects of vasoconstriction in septic shock are reported according to the involved pathophysiologic mechanism. The impact may vary according to the time of administration (early vs. late) and type and dose of vasopressor agent. It may also be affected by the density and sensitivity of vasopressor receptors, which varies across beds and according to patient's condition. *LV* left ventricle, *MAP* median arterial pressure, *depends on the vasopressor agent

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Declarations

Conflicts of interest
DDB: Edwards Lifesciences, Philips, Baxter, Viatris, Pharmazz. LH: Edwards Lifesciences. XM: Getinge, Baxter, AOL.

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